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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,366	09/19/2003	Fen Huang	34506.143	8954

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,366	HUANG ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-45 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-25 and 40-45 in the paper of 5/9/2006, is acknowledged. Applicants further election of RNase inhibitor proteins derived from mammalian sources in general, and derived from human placental sources and from recombinant sources and RNase A is also acknowledged. Applicants statements that these additional elections were for species are acknowledged, however, it is noted that these additional restriction requirements were in fact made as restriction requirements and not species election requirements.

Applicant's traversal of the requirement is found persuasive and claims 26-39 are included in the examination of claims 1-25 and 40-45.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosure statement, filed on 10/28/2004, are acknowledged. Those references considered have been initialed.

Claim Objections

Claims 5 is objected to because of the following informalities:

Claims 5 recite "recombinant human placental sources". This is interpreted as "recombinant sources of human placental " and it is suggested that this be amended to more accurately reflect such an interpretation.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-45 are directed to all possible methods of protecting and storing RNA or performing RT-PCR comprising the claimed combination of RNAase inhibitors, DTT and heat. The specification, however, only provides those methods encompassing the use of DTT, heat and either rat or human RNAsin, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the disclosed species. The specification also fails to describe additional representative species of RNAase inhibitor proteins for use in the claimed methods by any identifying structural

characteristics or properties necessary to ensure the successful use of these inhibitor proteins. Given this lack of additional representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods of use of rat or human RNAsin, does not reasonably provide enablement for the claimed methods of use of any RNAase inhibitor proteins . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-45 are so broad as to encompass any method of protecting and storing RNA or performing RT-PCR comprising the claimed combination of DTT and heat and any RNAase inhibitor protein. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods of use of any RNAase inhibitor protein broadly encompassed by the claims, including those methods of use of variant RNAase inhibitor proteins from any source. The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the RNAase inhibitor proteins used by the claimed methods. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity (i.e. functionality in combination with DTT and heat) requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those claimed methods involving the use of human and rat RNAsin.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to

modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass those methods of use of all modifications and fragments of any RNAase inhibitor protein, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the desired activity; (B) the general tolerance of RNAse inhibitor proteins to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a RNAase inhibitor protein with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the necessary activity for the claimed methods and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those methods of the claimed genus having the desired result.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including those methods of use of any RNAase

inhibitor protein of variant thereof. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 10-17, 18-25, 26-32, 33-39 and 40-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murthy et al. (Biochem J. Vol 281, pp 343-348, 1992) and Ambion (WO 00/17320, 3/30/2000).

Murthy et al. teach studies on the sensitivity of monomeric and dimeric forms of bovine seminal ribonuclease to human placental ribonuclease inhibitor, Murthy et al. specifically teach that the pretreatment of Bovine seminal RNAase BS-1 with 5 mM dithiothreitol (DTT) it exhibited greater inhibitor sensitivity to human placental RNAase inhibitor, presumably as a result of its partial monomerization on exposure to DTT. Murthy et al. further teach the above methods of pretreatiing RNAase with DTT involving incubating the mixture for 15 minutes at 37°C. Murthy et al. further teach that

multiple species of inhibitor-responsive RNAases reported in the literature may include dimeric and monomeric structures, including RNAase A.

Ambion (WO 00/17320) teach methods and reagents for inactivating ribonucleases comprising the treatment of ribonucleases with a reducing agent such as DTT (0.5 to 500 mM) and heat. Ambion teach that the taught methods may be applied to a variety of molecular biology reagents, including RNA samples, which may be contaminated with ribonuclease to protect an RNA from being degraded when incubated with the reagent. Ambion further teach the inactivation of Ribonucleases from crude cellular extracts to protect the full length cellular RNA from degradation, such that the RNA is suitable for several different analyses. Taught methods include the lysis of cells in cell lysis buffer (1X PBS containing 20 mM DTT and 0.1 mM EDTA) followed by heating of the cell suspension to 75°C for 5 minutes. Ambion further teach methods of reverse transcription followed by the polymerase chain reaction (RT-PCR) of the above generated RNAse inhibited samples.

One of skill in the art at the time of filing of the instant application would be motivated to combine the methods and teachings of both Murthy et al. and Ambion to perform a method for protecting or storing RNA from enzymatic degradation by RNAases, comprising the combination of a first solution containing RNA or that which RNA will be subsequently added, with a second solution comprising an RNAase inhibitor protein, such as human placental RNAase inhibitor in a solution with dithiothreitol (DTT) and then heating the mixture to a temperature of 60°C to 90°C for 3 to 20 minutes and then cooling and storing the mixture in an air-tight container, as a

means of isolating RNA from a crude cellular extract. Such methods include those involved in the protection of any RNA from any source such as plant, animal or bacteria, as all of these are sources of RNAses and also to all reagents which will come in contact with the isolated RNA, such as PCR buffers and the such. The motivation for the combination of the methods taught by Murthy et al. (i.e. the use of Ribonuclease inhibitor and DTT to inactivate RNAases) and the method taught by Ambion (i.e. the use of DTT and heat to inactivate RNAses) is based on the high sensitivity of RNA to the rapid degradation by various RNAses. This motivation is further enhanced by the durability and prevalence of the variety of RNAases in nature as taught by Murthy et al. One of skill in the art is motivated to use samples prepared in such a fashion as substrate for the nucleic amplification reactions including RT-PCR, as a means of amplifying specific RNA transcripts for further analysis. The expectation of success is high based on the high degree of knowledge in the art and the results of both Murthy et al. and Ambion whose method each employ overlapping concentrations of DTT.

Thus claims 1-8, 9-15, 16-22, 23-28, 29-35 and 36-43 are obvious over Murthy et al. and Ambion.

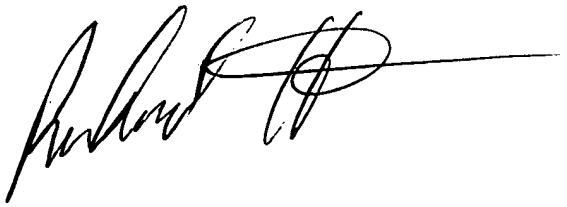
Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh
7/20/2006